Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism

Published: 02-07-2014
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The primary efficacy objective is to assess the incidence of symptomatic recurrent venous thromboembolism.The secondary efficacy objective is to assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON47378

Source
ToetsingOnline

Brief title
EINSTEIN Junior Phase III

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
blood clot, thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer B.V.

Intervention

Keyword: efficacy and safety, pediatric study, rivaroxaban, venous thrombosis

Outcome measures

Primary outcome

Assessment of incidence of symptomatic recurrent venous thromboembolism.

Secondary outcome

- Assessment of all symptomatic recurrent venous thromboembolism and

asymptomatic deterioration on repeat imaging

- Assessment of the incidence of over major and clinically relevant non major

bleeding

- Characterize the pharmacokinetic/pharmacodynamics profile of rivaroxaban

Study description

Background summary

Treatment with heparins and VKA (vitamin K antagonist) has several unsatisfying aspects. For heparins, this includes the requirement for intravenous or subcutaneous injection and monitoring of the activated partial thromboplastin time (aPTT). For VKA, this includes a slow onset and offset of action, a narrow therapeutic window requiring frequent INR (international normalized ratio) monitoring, and subsequent dose adjustments, caused by food and drug interactions. An oral anticoagulant drug that requires no monitoring of its effect, with a rapid onset of action and a high benefit-risk ratio is of considerable interest for the pediatric population.

Study objective

The primary efficacy objective is to assess the incidence of symptomatic recurrent venous thromboembolism.

The secondary efficacy objective is to assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging.

The principal safety objective is to assess the incidence of overt major and clinically relevant non major bleeding.
An additional objective is to characterize the pharmacokinetic / pharmacodynamics profile of rivaroxaban.

Study design

This is a multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age- and body weight-adjusted rivaroxaban regimen in children with acute venous thromboembolism.

Intervention

Randomization into three arms:

1. Rivaroxaban (suspension) once, twice or three times daily (depending on body weight) for at least 3 months up to maximum 12 months (for children aged < 2 years with catheter related thrombosis: at least one month up to maximum of three months).

2. Standard treatment in the Netherlands, consisting of VKA (tablets) or LMWH (injections) for 3 months up to a maximum of 12 months

Children aged 0 months - 6 years will be given the rivaroxaban suspension, children aged 6 - 12 years will be given the choice between rivaroxaban tablets or suspension, children aged 12 - 18 years will be given the rivaroxaban tablets.

Protocol V3.0: all children will receive the rivaroxaban suspension; tablets are no longer used (sufficient data collected).
Protocol V4.0: all children will receive the rivaroxaban suspension; tablets are no longer used (sufficient data collected).
Protocol V5.0: all children will receive the rivaroxaban suspension; tablets are no longer used (sufficient data collected).

Study burden and risks

The study has 5 to 8 planned visits, depending on the elected study duration. Patients randomized to the rivaroxaban-arm, who receive a three times daily dose, will have an additional visit (visit 1A).

At the end of the initial 3 month treatment period, the decision is made to stop study treatment or to continue for an additional 3 months (for children aged < 2 years with catheter related thrombosis this will be decided after 1 month). The need to continue with anticoagulant treatment will be assessed every 3 months (for children aged < 2 years with catheter related thrombosis every month) for up to 9 additional months (up to 3 months for children aged < 2 years with catheter related thrombosis).

Regardless of the duration of study treatment (3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. If the child is treated with rivaroxaban, 4 blood samples (children 12 kg and above 12 kg) or 6 blood samples (children below 12 kg) will be taken for PK/PD evaluation and if the child is treated with VKA, at least 1 blood sample will be taken every 2 weeks for monitoring anticoagulant treatment.

Diagnostic imaging test will be obtained at baseline and if clinically feasible will be repeated at the end of the initial 3 month treatment period (after one month for children aged < 2 years with catheter related thrombosis).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. - Children aged birth to < 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. However, children aged birth to < 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days.
For children younger than 6 months:
- Gestational age at birth of at least 37 weeks.
- Oral feeding/nasogastric/gastric feeding for at least 10 days.
- Body weight *2600 g ;2. Informed consent provided and, if applicable, child assent provided

Exclusion criteria

1. Active bleeding or bleeding risk contraindicating anticoagulant therapy;2. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 ;3. Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) > 5x upper level of normal (ULN) or total bilirubin (TB) > 2x ULN with direct bilirubin > 20% of the total;4. Platelet count < 50 x 109/L;5. Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure > 95th age percentile;6. Life expectancy < 3 months;7. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), including but not limited to all human immunodeficiency virus protease
inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically ;8. Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine;9. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2014
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xarelto
Generic name:	rivaroxaban
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2014
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	16-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	30-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000565-47-NL
CCMO	NL49368.078.14